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Efficacy and tolerability of lamotrigine in Juvenile Myoclonic Epilepsy in adults: A prospective, unblinded randomized controlled trial

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ABSTRACT

Purpose: Controlled randomized studies recommending the clinical use of lamotrigine in adult populations with the diagnosis of Juvenile Myoclonic Epilepsy are still lacking. To compare the efficacy and tolerability of lamotrigine versus valproate in adult patients with JME.
Methods: This was a prospective, randomized, controlled, pragmatic, long-term and open-label treatment trial. Patients were randomized to use valproate or lamotrigine. The primary end points of the study were: (1) time from randomization to treatment failure (withdrawal); (2) time from randomization to seizures remission. Secondary ending points were: (1) frequency of clinically important adverse events and (2) change in the QOLIE-31 after randomization. The definition of seizure remission was based on disappearance of all seizure types and EEG discharges.
Results: We found that the time to withdraw treatment after randomization was not significantly different in lamotrigine and valproate groups. Long-term seizures freedom was equal in the both groups of the trial; only 8 (19.1%) patients randomized to lamotrigine and 6 (19.4%) randomized to valproate were not seizure free after 4 months of treatment. Between 17.03% (lamotrigine) and 35.3% (valproate) of patients reported adverse reactions at some point in the intention-to treat study ($p = 0.07$). All subscales of the QOLIE-31 questionnaire, except that related to side effects of medication, improved more than 5 points with respect to baseline period in both groups
Conclusion: Lamotrigine is effective in adult patients with Juvenile Myoclonic Epilepsy and better tolerated than valproate, although the incidence of idiosyncratic reactions could be a cause of concern.

1. Introduction

Juvenile Myoclonic Epilepsy (JME) represents the most common form of idiopathic generalized epilepsy (IGE).[1]

JME seizures respond well to antiepileptic drugs (AEDs), particularly valproate. The SANAD (Standard and New Antiepileptic Drugs) study reported that valproate was the most effective and best-tolerated first-line AED for patients with IGE, including JME, when it was compared to lamotrigine and topiramate (TPM).[2]

Valproate is the first-line drug in men with JME, but in female population, lamotrigine (LTG) is preferred due to the teratogenic and endocrinologic side effects such as polycystic ovary syndrome and weight-gain associated to valproate. Recent data suggest that it may soon be used as first line treatment[2–5]; nevertheless, some studies have reported aggravation of JME with LTG.[6–12]

LTG is a phenyltriazine derivative which acts through inhibition of voltage-activated sodium channels and possibly calcium channels, preventing the release of glutamate.[5] LTG is effective in controlling generalized tonic–clonic seizures (GTCS) and absence seizures[13–17]; while there are some reports of myoclonic seizure exacerbation.[6,7] Nevertheless, many studies performed over the recent years have demonstrated the clinical utility of this AED for the treatment of JME.[6–9]

Demonstration of LTG's usefulness in JME is especially important for women who live in developing countries, due to the lack of levetiracetam, zonisamide and TPM[18–20] and also for those female or male patients who have had adverse reactions to valproate or who have contraindications for its use.

That's why, in some scenarios, LTG has become the first line AED in women with JME of childbearing potential and even in men. Nevertheless, to our knowledge, open labeled, prospective, controlled randomized trials, that allow recommendation of LTG for adult population with JME in clinical practice, are still lacking.

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We carried out the present trial to determine the efficacy and tolerability of lamotrigine in adult patients with JME.

2. Methods

2.1. Study design

This was a prospective, randomized, controlled, pragmatic, long-term, open-labeled treatment trial. The study was carried out at the National Institute of Neurology and Neurosurgery in Havana, Cuba.

2.2. Study population

Patients from the whole country are referred to our institution which is a tertiary center. The epilepsy section offers medical assistance to 1089 patients with epilepsy. Juvenile Myoclonic Epilepsy represents approximately 10.3% of all epileptic syndromes treated in our institution.

2.3. Diagnosing process and follow-up

All subjects were enrolled in the study sequentially from the outpatient clinic. The first patient was included on January 2nd 2008, and randomization continued up to June 30th 2010. Attempts were made to follow all patients for at least 2 years, but those who did not return to the outpatient clinic, were included in until the moment they were evaluated for the last time (ITT protocol). Trial design can be seen in Fig. 1.

All patients and two of their relatives were interviewed by experienced epileptologists concerning seizure types, age at seizure onset, seizure precipitant factors, possible circadian rhythm of seizures and previously used medications.

In all the patients where Juvenile Myoclonic Epilepsy was suspected, a routine 21-channel EEG was obtained, according to the international 10–20 system employing a Medicid EEG digital machine, at the moment of entering the study and after 2 years of follow-up. All patients were sleep deprived the night before to EEG performance. At least 10 min of sleep were recorded in each patient, which primarily resulted in early sleep stages recording (stages 1 and 2 of non-REM sleep) and only rarely stage 3 non-REM sleep was seen. EEG recordings had a mean duration of approximately 30 min.

Taking into account seizure semiology and the electrographic pattern obtained, the diagnosis of JME was made by two epileptologists according to the ILAE criteria.[13] Seventy-two patients (100%) had myoclonic seizures, 45 patients had GTCS (62.5%) and absence seizures were reported in only 27 (37.5%).

2.4. Inclusion criteria

Patients were included in the study if they had past history of two or more generalized myoclonic seizures. Tonic–clonic or absence seizures in the previous years were also taken into

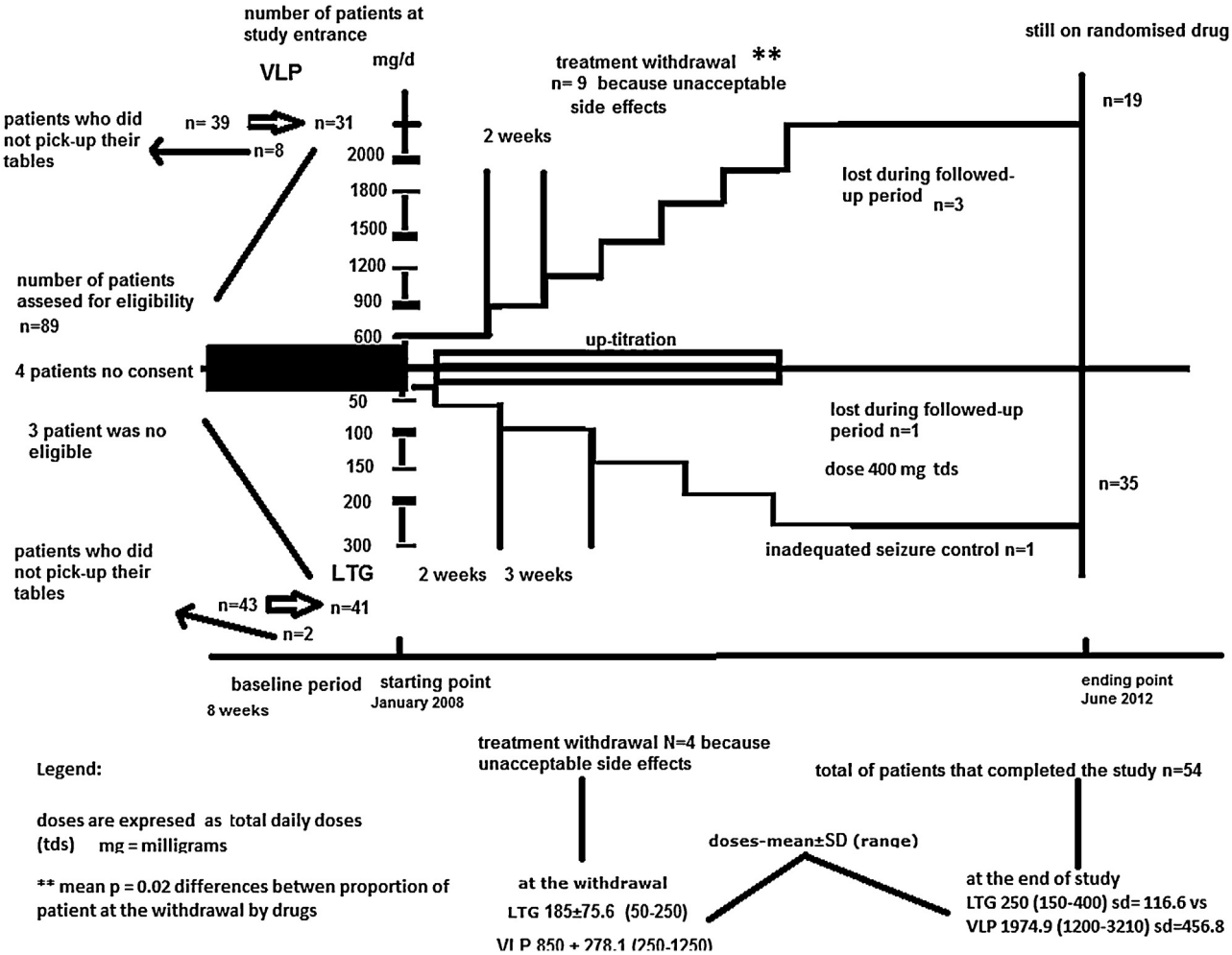

Fig. 1. Trail profile. The total number of patients that withdrew from treatment for any reason was 12/31 in the valproate group and 6/41 in the lamotrigine group (differences between two proportions), $p = 0.02$.

consideration. As myoclonic seizures are mandatory for JME diagnosis, all enrolled patients had a past history of this seizure type. However, subjects without absences or tonic–clonic seizures were also included in the study. These criteria allowed inclusion of patients with newly diagnosed epilepsy and patients who had been previously treated under monotherapy or politherapy regimens (as long as the treatment failure was not due to one of the drugs employed in the trial).

2.5. Exclusion criteria

Patients with insufficient documentation of seizure frequency, poor compliance, progressive neurological diseases, severe psychiatric disorders, drug or alcohol abuse, systemic disorders, laboratory abnormalities or those who were pregnant or breastfeeding, were not eligible for the study.

2.6. Follow-up

Those patients who were taking at enrolment antiepileptic drugs that worsen Juvenile Myoclonic Epilepsy, such as carbamazepine or phenytoin, were instructed to drop the doses out slowly during the following 3 weeks and afterwards, they should return to the outpatient clinic to start with valproate or LTG.

After the diagnosis was confirmed, they were interrogated concerning the number of seizures in the last 2 months (baseline period). All seizure types were scored: myoclonic, absences or GTCS. An information booklet describing the seizure types was given to all patients and their relatives in order to obtain an adequate score. The booklet summarized the following information:

- Myoclonic seizures are considered as shock-like movements, irregular and arrhythmic sudden contractions of proximal and distal muscles, mainly of the upper extremities; sudden involuntary movements making the patient prone to drop things or look clumsy.
- Absence seizures should be described by a relative or a witness. Absences are characterized by sudden onset and interruption of ongoing activities, blank stares, slowing or speech interruption; standing transfixed and unresponsive when spoken to. Additionally, as the patient may not stop his or her activities, absences seizures are considered if the relative is aware of slowing down of speech.
- GTCS are considered as convulsions.

As the patients were prospectively studied, baseline seizure rate was estimated from patient's memories at study entrance; but subsequent seizure rate was calculated from seizure diaries. No statistical analyses were made to compare the number of seizures per month before and after treatment. The past history of seizures was used only to train patients and relatives on the semiology of different seizure types.

The epileptologists randomized patients with a computer program using a minimization procedure. Three patients were not eligible and 4 did not sign the informed consent. Participating patients (eligible) were randomly allocated to valproate ($n = 39$) or LTG ($n = 43$). Before initiating treatment, the epileptologists explained the possible side effects of each medication. Then, patients were instructed to pick up the medication every month at the hospital pharmacy. A pharmacologist gave the patients all the pills every month without any cost. Eight patients randomized to Valproate regimen and 2 patients randomized to the LTG group were not treated, and were dropped out of the study because they did not pick up their medication. Those patients, who were not included in the study, were followed in the corresponding secondary centers. Thus, the total number of patients assigned to LTG was higher than the number of patients in the valproate group, in spite of having been correctly randomized. Finally, 31 patients were in the valproate arm and 41 in the LTG arm.

Data from patients who withdrew from the study for any cause were included in the analyses up to the moment of their last follow-up visit.

Although the prescribed drug was determined by randomization, drug dose was that prescribed by the physicians in their everyday practice. The initial maintenance dose, and any subsequent increment or decrement was decided by the epileptologists, but the rate of titration was aided by guidelines (Table 1). The mean doses of each drug at the end of the study and at withdrawal are showed on the right inferior part of Fig. 1.

The aim of treatment was to control seizures with the minimum effective dose of the drug. Visits were scheduled approximately once per month. Additional visits were allowed according to patients' or families' needs. The doses of the AED were increased in those patients in whom new seizures appeared (as is usual in clinical practice). In those cases, dose increments consisted of 200 mg for the valproate group and 50 mg for the lamotrigine group.

Therapy failure was considered when intolerable side effects or ongoing seizures occurred, in spite of an adequate dose, and if the patients could not be followed during 3 months. All of those patients were dropped out from the study.

Due to the fact that we could not measure plasma concentration of AEDs, to consider therapy failure of lamotrigine or valproate, the dose should be titrated to the maximum orally tolerated doses when it was necessary. Those patients with treatment failure continued their follow-up in our outpatient clinic and they were crossed-over to valproate if they were under treatment with lamotrigine and to lamotrigine if they were under treatment with valproate (the results of the crossover trial will not be described in the present study).

To determine seizure rate, all seizures written in the patient's diaries were recorded by the epileptologists in every visit. Only episodes with semiologic characteristics compatible with absence, myoclonic or GTCS were registered and considered for the statistical analysis. Thus, episodes different to these seizure types were ruled out and not analyzed.

2.7. Evaluation of efficacy

The primary end points of the study were: (1) time from randomization to treatment withdrawal (stopping the randomized

Table 1
Guideline for titration of medications during follow-up.

Medication (dose/weeks) Valproate	Week	Week	Week	Week	Week	Week	Week
	1–2	3–4	5–6	7–8	9–10	11–12	13–14
Medication (dose/weeks)	200 mg/3 times/day	400 mg/3 times/day	600 mg/3 times/day	2000 mg daily	3000 mg daily	3000 mg daily	3000 mg/Daily
	Week	Week	Week	Week	Week	Week	Week
Lamotrigine	1–3	4–7	8–11	12–15	16–19	20–24	25–27
	25 mg single dose	25 mg/times/day	50 mg/2 times/day	50 mg/3 times/day	100 mg/times/day	250 mg/daily	300 mg/daily

drug because of inadequate seizure control, intolerable side-effects, or both; whichever was the earliest) and (2) time from randomization to seizure remission. Secondary end points of the study were: (1) frequency of clinically important adverse events and side-effects emerging after randomization, (2) quality of life outcomes, (3) number of seizures evaluated at 3, 6 and 24 months after treatment was initiated.

2.8. Seizure outcome assessment

Seizure outcome was assessed through clinical visits. The baseline seizure rate was considered as seizure frequency at 2 months before enrolment. For each patient the number of myoclonic, absence and GTCS per month during follow-up was calculated taking into account seizure diaries.

Only patients who reported having no seizures and with normal EEG recordings at the end of the study (2 years after study entrance), were considered to be seizure free.

Normal EEG at the end of the research was considered in those cases with EEG recordings obtained after 6 h of sleep deprivation, during 30 min, in which normal background activity with total absence of generalized polyspikes and spikes and waves and photoparoxysmal activity were reported.

Inadequate seizure control was considered in those patients who continued with some seizure types in spite of adequate dose regimens and treatment compliance. Because measurement of drug plasma levels was not feasible, an adequate dose regimen was operationally considered when maximal tolerated dose was reached or when more than 2000 mg/day in the valproate group or more than 300 mg/day in the LTG arm was achieved.

2.9. Quality-of-life assessment

All patients who were cognitively able to give informed consent and who could complete a quality-of-life inventory received the QOLIE-31 questionnaire within the 4 weeks previous to randomization. The Quality of Life questionnaire (QOLIE-31) consists of a 31-item scale that assesses seizure worry, well-being, energy or fatigability, social functioning, cognitive functioning, side effects of medication and overall quality of life.[14] The scoring scale extends from 0 to 100, with the highest score reflecting the best quality of life.[14] The questionnaire was administered when the patients were enrolled in the study and after 2 years of follow-up.

2.10. Adverse events assessment

In each visit the patients and their relatives were requested to report any symptom felt after drug treatment was initiated. If so, adverse event was considered if the referred symptom had been previously described for valproate of for LTG. In case symptoms had not been described for the medication under analysis, they were taken into account if no other explanation was found.

2.11. Compliance assessment

Treatment compliance was assessed on the basis of returned tablet counts, and it was defined as tablet consumption within 80–120% of the prescribed dose.

2.12. Ethics

The study was conducted according to the Declaration of Helsinki's criteria and no funding was received from pharmaceutical companies. The patients gave their informed consent to participate in the study, which was approved by the local ethics committees.

All authors had full access to the data and took responsibility for its integrity and for the accuracy of the data analysis. The corresponding author had the final responsibility for the decision to submit for publication.

2.13. Statistical analysis

We decided to assess whether treatment with LTG had advantages in tolerability and safety, or even if there were no immediate advantage, if it could be an alternative or second-line therapy (*test of equivalence*). Due to the above mentioned design, instead of the conventional test of significance, statistical analysis is based on confidence intervals (CIs) that define a range for the possible true differences between the treatment groups. Taking this paradigm into account, the two studied drugs were considered as equivalent if the entire CI for their difference lies within the pre-set clinically relevant range of equivalence.

Pre-set clinically relevant range of equivalence: taking into account that valproate is the first eligible drug to treat patients with JME and its proved efficacy in this epileptic syndrome, the number of seizures evaluated at 3, 6 and 24 months after treatment was initiated, should not be statistically different between randomized groups in terms of CI.

The statistical analysis included intention to treat analysis (ITT) and per protocol analysis (PPA). Intention to treat analysis considered all patients who received at least one drug dose. For patients who dropped out from the study the analysis included all available data until patients withdrew from the study; whereas per protocol analysis included only those patients who finished the follow-up.

2.14. Primary end point

The time from randomization to treatment withdrawal (stopping the drug the patient was randomized to because of inadequate seizure control, intolerable side-effects, or both; whichever was the earliest) (ITT) and the time from randomization to seizure remission (PPA) were analyzed using the Kaplan Meier method, comparing the mean time with each seizure type during the follow-up period.

To analyze the secondary ending point, ANOVA (Wilk Lamda) and *T* tests were used to compare continuous variables. Mann–Whitney was used to compare discontinuous variables. Qualitative variables were compared using the Chi square test. Side-effects of medication were analyzed comparing the proportion of patients who reported/experienced side effects. To evaluate the differences between rates of adverse events and proportions of patients who dropped-out from the study in both randomized groups, we tested the difference between proportions. This was computed according to the following formula:

$$/t\,\text{value}/ = \text{square}(N1 * N2)/(N1 + N2) * / p1 - p2/\text{square}[p * q] \quad \text{where } q = 1 - p \text{ and } p = (p1 * N1 + p2 * N2)/(N1 + N2).$$

For all measurements only p values below 0.05 were considered significant.

3. Results

3.1. Demographic, clinical and electrographic results

Forty-one patients were randomized to the lamotrigine group and 31 to the valproate arm. Twenty-five (30.5%) out of 82 patients

had been treated with carbamazepine without seizure control (mean doses 970 ± 230 mg/daily). Thirty-eight (46.3%) had been treated with carbamazepine associated with clonazepam and they reported total control of their GTCS, although myoclonic seizures had continued (mean doses 670 ± 135 mg/daily vs. 1.1 ± 0.3 mg/daily). Two patients (2.4%) had received phenytoin but they had discontinued the medication as they noticed seizure worsening (mean doses 150 ± 50 mg/daily). Seventeen patients (20.7%) had never received any medication before.

Patients were aged between the second and fifth decade of life at study entrance. The predominant seizure type in both groups was myoclonic jerks. Both groups of patients had a history of convulsions for more than 10 years. In all patients the interictal electrographic patterns were characterized by the presence of generalized polyspikes, and spikes and waves; although focal paroxysmal activity was documented in approximately 19%. Thus, treatment groups were well balanced for demographic, clinical and electrographic factors (Table 2). There was no statistical difference between male/female rates by groups.

3.2. Follow-up by groups of treatment

As expected, doses associated with treatment failure due to unacceptable adverse events were consistently lower than doses associated with treatment failure due to an inadequate seizure control (Fig. 1, see up-titration scale). In spite of the fact that, dosing was left to the physician's usual practice, the total doses of VPA were similar in each group and they were not lower in the female group, $p > 0.05$.

Thirteen cases declined further follow-up during the study because of unacceptable side effects: 9 in the valproate arm (29%) and 4 in the lamotrigine arm (9.8%), ($p < 0.05$). Two out of 4 patients in the LTG arm suffered from Stevens–Johnson Syndrome (SJS). One of them was a 23-year old female who presented the SJS 3 weeks after the initial doses of LTG. The total daily doses at SJS presentation was 50 mg/day. The second one was a 25-year old black male, who presented SJS 5 weeks after the initial doses. Total daily doses in this case at SJS presentation were 100 mg/day. Both patients were hospitalized and treated with prednisolone (60 mg/day for 7 days) and lamotrigine was changed for valproate. Both were delivered from our hospital after complete resolution of the syndrome (12 and 11 days after admission, respectively).

Four patients were lost from follow-up for other reasons, and one patient was dropped out because of inadequate seizure control in spite of adequate compliance (the patient had been allocated to the lamotrigine group). The total number of patients that withdrew from the study for any reason was 12/31 (38.7%) in the valproate group and 6/41 (14.6%) in the lamotrigine group. Statistical analysis showed that the percentage of patients who dropped out was significantly higher in the valproate arm (Fig. 1).

3.3. Treatment failure events

To achieve clinical benefit and complete seizure remission in the responder group, it was unnecessary to reach the maximal tolerated doses of lamotrigine or valproate in any case (Table 2).

Analysis of treatment failure due to unacceptable adverse events (Table 3) indicates that lamotrigine was less associated with unacceptable adverse events than valproate ($p < 0.05$). Otherwise, lamotrigine was not significantly less effective than valproate for the treatment of myoclonic, absence and tonic–clonic seizures (see Kaplan Meir survival curve in Fig. 2A–C). Nevertheless, in one patient randomized to lamotrigine treatment, myoclonic seizures worsened with respect to the starting point seizure rate (Fig. 1).

The time to treatment withdrawal for any reason was lower in the valproate group compared to the LTG group, but without statistical significance (Table 4). Total seizures per group of randomization during follow-up (3, 6 or 24 months) were equivalent and CIs for seizure frequency during follow-up in the LTG and valproate groups were similar (Table 4). Three patients in the valproate group (9.7%) and 4 (9.7%) in the LTG group, did not reach total control of myoclonic seizures (Table 4).

Seizure remission rates at the end of the follow-up period are shown in Fig. 3A. A high proportion (more than 80%) of patients achieved total seizure control after 4 months treatment. The proportion of patients who remained with seizures after treatment was not significantly different in the LTG and valproate groups ($p > 0.05$). Otherwise, 2 patients (4.8%) randomized to the LTG group still showed polyspikes and spikes and waves in the EEG after 2 years of treatment, whereas all cases (100%) in the valproate arm had EEG normalization ($p > 0.05$) (Table 4).

3.4. Compliance assessment

Two patients (6.5%) in the valproate arm had a total tablet consumption of approximately 80%, the rest had a tablet consumption ranging from 90% to 100%. Three patients in the LTG group (7.3%) had a total tablet consumption of approximately 80%; the rest had 100% compliance (Table 5).

3.5. Adverse events

An intention-to-treat approach summarizes adverse events associated with the randomized policy. As patients could not have treatment changes during follow-up, this approach clearly shows adverse events attributable to specific drugs. Therefore, in Table 5 we present adverse event rates for both intention to treat and per protocols. Seven patients (17.03%) in the LTG arm and 11 subjects (35.3%) in the valproate arm reported adverse events at some point in the intention-to treat study. This difference reached statistical significance ($p = 0.04$). Among the individual symptoms, the most commonly reported were: allergic rash (4 patients; 9.8%) and sleep disturbances (3 patients; 7.3%) for the LTG arm; and weight gain (5 patients; 16.1%), alopecia (3 patients; 9.7%), dyspepsia (9.7%) and nausea (9 patients; 29.1%) in the valproate arm. Rash was a prominent non-central nervous system symptom, especially with lamotrigine (4 patients with rash; 2 of them with Stevens–Johnson syndrome). This adverse event was associated with treatment failure in the lamotrigine group; whereas for valproate, weight-gain was the most common symptom causing treatment withdrawal.

Table 2
Incidence of adverse events leading to drug discontinuation during treatment period in the intention-to-treat population.

Medication	Number of patients with adverse events	Number of patients without adverse events	Total
Valproate[a]	9 (12.5)	22 (30.6)	31 (43.1)
Lamotrigine	4 (5.6)	37 (51.4)	41 (56.9)
Total	13 (18.1)	59 (81.9)	72 (100)

Chi-square test (DF = 1) = 4.4, $p = 0.03$.
[a] Number of patients with adverse events (comparison between valproate and lamotrigine).

Table 3
Clinical and demographic characteristics of randomization groups at study entrance.

Clinical and demographic variables	Lamotrigine $n=41$ (means ± SD [range])	Valproate $n=31$ (means ± SD [range]))
Age at seizure onset (years)	16.3 ± 6.1 [9–23])	15.3 ± 7.3 [8–23])
Age at study entrance (years)	26.8 ± 10.9 [15–57]	27.3 ± 12.6 [15–56]
Weight at study entrance (kg)	71.5 ± 13.9 [48–89])	64.6 ± 12.1[49–86])
Number of tonic-clonic seizures (per month) median [range]	1 [0–10]	2 [0–12]
Number of absences seizures (per month) median [range]	4 [0–60]	2 [0–78]
Number of myoclonic seizures (per month) median [range]	5 [2–60]	6 [3–60]
Time from seizure onset to study entrance (years)	13.9 ± 11.1	12.9 ± 9.1
EEG		
Number of patients with generalized polyspikes and spikes and waves	41 (100%)	31 (100%)
photosensitivity +	21 (51.21%)	18 (58.6)
Number of patients with generalized polyspikes and spikes and waves at the end of the follow-up	2 (4.8%)	0 (0%)
Focal activity +	8 (19.5%)	6 (19.3)
Gender M/F (#/%)	15 (36.6)/26 (63.4)	10 (32.3)/21 (67.4)
Doses employed during follow-up (mg tds) mean ±SD (range) M/F (ITT)	279 ± 159 (150–400)/249 ± 179 (150–400)	1570 ± 345 (900–3000)/1550 ± 450 (900–2700)
QOLIE-31 (total)	69.5 ± 13.3	62.9 ± 17.85

p values less than 0.05 are marked with *. ITT means intention to treat analysis.

The total quality of life score in the LTG arm improved 7.3 points and 12.3 points in the valproate arm after 2-years of follow-up (Table 6). All subscales of the QOLIE-31 questionnaire except the subscale related to side effects of medication improved more than 5 points after treatment. On the other hand, there were significant differences for the outcome assessed by the response rate in (energy/fatigability, global quality of life, emotional well-being, cognition functioning) in the valproate group and in emotional well-being, energy/fatigability in the LTG group (Fig. 3B and C). The subscale "side effects of medication" worsened in both groups because the patients had not been taking these drugs at the starting point and this subscale had been scored as 100. There were no significant differences in the remaining subscales between the scores at the starting point and at the end of follow-up, between both study groups.

4. Discussion

Valproate is considered the first line antiepileptic drug for patients with Juvenile Myoclonic Epilepsy (JME). Three other antiepileptic drugs have been employed (levetiracetam, topiramate and zonisamide), which are also said to be effective in generalized epilepsies.[2,5]

In developing countries, many of the above mentioned medications are not part of the therapeutic approach,[17–20] because of their high cost and poor availability; but lamotrigine is available in our country. Thus, our study constitutes a good example of the therapeutic scenarios that mirror what happens in other developing countries.

Due to the fact that lamotrigine has been associated with seizure exacerbation in JME,[2,21,22,10] the therapeutic alternatives in developing countries are scarce. In such cases clonazepam administration in small doses (0.5–2 mg at night) is probably the most effective treatment for myoclonic jerks; but clonazepam alone may not suppress GTCS (generalized tonic–clonic seizures).[21] Nevertheless, in mild JME with myoclonic jerks only, clonazepam alone may be recommended.

Thus, physicians prescribe valproate in spite of its well known teratogenic and cognitive side effects in children exposed in uterus to this antiepileptic drug.[20,23,24] Taking into account that differences in efficacy among AEDs in newly diagnosed patients with epilepsy are difficult to detect, according to the review published by Patrick Kwan and Martin Brodie, we decided to assess whether treatment with LTG had advantages in tolerability and safety with respect to valproate; or even if there were no immediate advantages, if it could be an alternative or second-line therapy (*test of equivalence*) for patients with JME.[22,10] We evaluated the effectiveness of LTG as a function of its efficacy and tolerability as it has been recommended.[24–27]

In our study we found that the time to withdrawal of lamotrigine after randomization was not significantly higher than valproate. The long-term seizure freedom was equal in the two arms of the study: only 8 (19.1%) patients randomized to lamotrigine and 6 (19.4%) to valproate were not seizure free after 4 months treatment.

When efficacy is similar between two drugs, their overall effectiveness is often determined by tolerability.[24] This is best measured by the rate of withdrawal of treatment because of adverse events. Taking this into account, lamotrigine was better

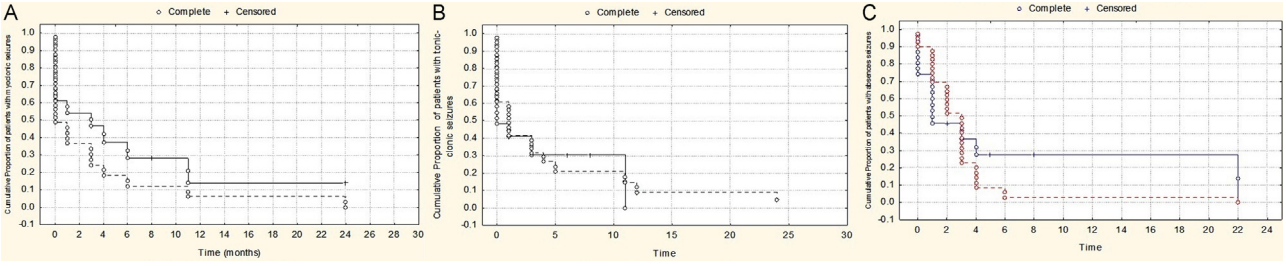

Fig. 2. (A) Cumulative proportion of patients with myoclonic seizures during follow-up. Valproate has been highlighted with continuous line and lamotrigine with discontinuous line. Log-Rank Test: WW = −2.141, Sum = 30.4, Var = 7.1. Test statistic = −2, $p = 0.07$. (B) Cumulative proportion of patients with tonic–clonic seizures during follow-up. Valproate has been highlighted with continuous line and lamotrigine with discontinuous line. Log-Rank Test: WW = 0.56, Sum = 37.1, Var = 9.2. Test statistic = .18, $p = 0.85$. (C) Cumulative proportion of patients with absence seizures during follow-up. Valproate has been highlighted with continuous line and lamotrigine with discontinuous line. Log-Rank Test: WW = 0.51, Sum = 35.2, Var = 8.2. Test statistic = .16, $p = 0.75$.

Table 4
Number of seizures during follow-up and time from randomization to withdrawal for any reason and to achieve EEG normalization.

Seizure types	Median (range) [IC] (valproate vs. lamotrigine)
Time to withdrawal	11 (3–20) vs. 12 (3–20) [9.2–13.3]; [8.5–16.3]*
Total seizures after 3 months treatment	6 (0–15) [1.2–9.3] vs. 8 (0–60) [1.7–11.3]*
Total seizures after 6 months treatment	1 (0–4) [0.8–2.8] vs. 2 (0–2) [1.1–2.9]*
Total seizures after 24 months treatment	0 (0–3) [0–1.8] vs. 2 (0–4) [1.03–1.4]*
Time to achieve EEG normalization (weeks)	24 (17–32) vs. 27 (20–38) [21–28.2]; [22–30.1]*,††

* $p > 0.05$.
†† Refers to 2 patients (4.8%) that continued with polyspikes and spikes and waves at the end of the study in the LTG vs. 0 (0%) in the valproate group (per protocol analysis).

tolerated than valproate (differences between the proportions of withdrawal rates was significantly higher in the valproate group). Also, the proportion of patients with any adverse event was higher in the valproate group. We found worsening in myoclonic seizures in only one (2.4%) of our patients randomized to the LTG arm. This percentage is very low; nevertheless, it is very important because of trauma risks associated with myoclonic seizures. Worsening of seizure rate with lamotrigine has been reported previously.[3,21,22,10]

An important concern is the high frequency of Stevens–Johnson Syndrome found in our study. In the presentation manufacturer's product information, the incidence of serious skin rashes, including Stevens–Johnson syndrome, and rashes requiring hospitalization is approximately 8 per 1000 in patients younger than 16 years receiving lamotrigine as adjunctive therapy for epilepsy.[28] In clinical trials of bipolar and other mood disorders, the rate of serious skin rashes was 0.8 per 1000 in adults receiving lamotrigine as initial monotherapy and 1.3 per 1000 in adults receiving lamotrigine as adjunctive therapy. Nevertheless, skin reactions like maculo-papular erythema were the most frequent, but less serious side effects found in patients treated with lamotrigine. Saetre et al. described up to 5% of cutaneous rash in patients taking lamotrigine for refractory partial epilepsy.[29] In the monograph written by Xiang-ging et al., they described lamotrigine as the antiepileptic drug that caused the highest incidence (about 10–12%) of skin reactions.[30] In the SANAD study the authors found 12% of skin reactions in the group of patients receiving lamotrigine as monotherapy; moreover the authors did not mention the number of patients with severe skin reactions or SJS, and they found that lamotrigine was associated to treatment failure in 4% of the patients.[2] Our results mirror the above mentioned studies related to rash occurrence and rate of drop out associated to lamotrigine, but the incidence of SJS was higher. The main risk factors associated with skin reactions, including SJS, with lamotrigine treatment are: patient's age (younger children are more susceptible than adults), rapid titration schedule and high initial doses.[2,28,31] We think that rapid titration schedule played an important role in the high incidence of SJS in our series. One of the two patients who presented SJS, increased the total dose to 50 mg in the third week of follow-up, instead of maintaining a regime of 25 mg daily and the other one increased the total daily dose to 100 mg in the fifth week, instead of continuing with 50 mg/day as we had proposed. Thus, it could account for the high incidence of SJS presentation in our study.

A significant problem and well-documented side effect linked to valproate but not to lamotrigine are the weight-gain and the endocrinologic abnormalities like (polycystic ovary syndrome) and amenorrhea. In our study 16.1% in the valproate group increased weight after treatment and 6.4% presented with amenorrhea. Nevertheless, we did not assess any hormonal or structural ovarian changes in women taking part in this study, so we cannot comment on a possible difference in endocrine side effects of the two drugs.

In both treatment groups the overall quality of life improved significantly. Nevertheless, unlike the lamotrigine group, a slighter improvement in certain domains of quality of life was observed in patients treated with valproate (cognitive functioning and global quality of life), and these advantages could be important because cognitive functioning was worse in the valproate group at the starting point than in the lamotrigine group. It is important to explain why the QOLIE-31 score improved more for VPA than LTG; in spite of the fact that adverse events were 2 fold higher for VPA. We think that the effect of valproate on emotional feelings could explain that result partially. Nevertheless, the comparison of QOLIE-31 between patients under treatment with LTG and valproate were made in per protocol analysis. Most of the patients with adverse events were dropped out of the study and the QOLIE-31 score at the end of the study was not available. In the case of valproate, nine patients were dropped drop out because of unacceptable side effects. Maybe this is the main explanation for the slight improvement in total QOLIE-31 score observed in the valproate group.

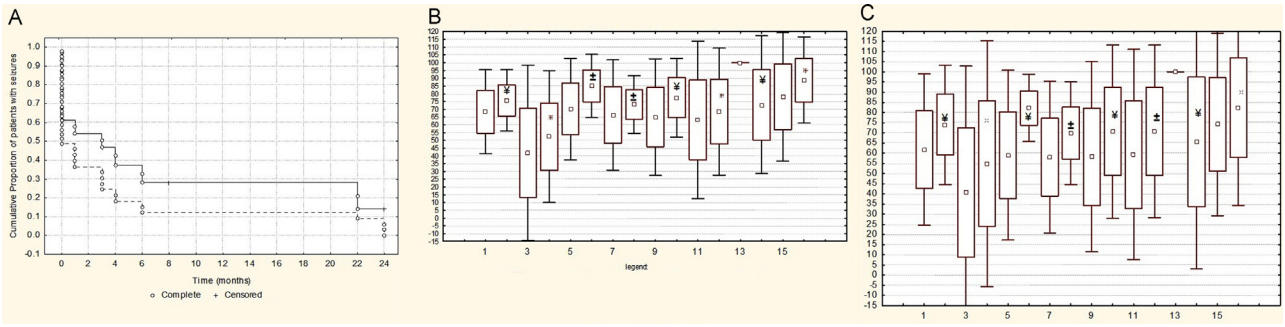

Fig. 3. (A) Cumulative proportion of patients with any seizure type during follow-up according to group of randomization. Cumulative Proportion of patients with seizures (Kaplan–Meier curve). Log-Rank Test: WW = −2.01, Sum = 29.4, Var = 5.2.Test statistic = −1.6, $p = 0.09$. Eight (19.1%) patients randomized to lamotrigine and 6 (19.4%) to valproic acid were not seizure free after 4 months treatment. (B) Quality of life at the beginning and after 2 years treatment with valproate. Mean, Mean ± SD, Mean ± 1.96*SD (before treatment, first bars vs. 2 years after treatment, second bars). (1) Total QOLIE, (3) seizure worry, (5) global QOLIE, (7) emotional well-being, (9) energy/fatigability, (11) cognition functioning, (13) side effects of medication, (15) social functioning. Statistical test: Wilcoxon Matched Pairs Test (*mean $p > 0.05$, ±mean $0.05 < p > 0.01$, ¥ $p < 0.01$). (C) Quality of life at the beginning and after 2 years treatment with lamotrigine. Mean, Mean ± SD, Mean ± 1.96*SD (before treatment, first bars vs. 2 years after treatment, second bars). (1) Total QOLIE, (3) seizure worry, (5) global QOLIE, (7) emotional well-being, (9) energy/fatigability, (11) cognition functioning, (13) side effects of medication, (15) social functioning. Statistical test: Wilcoxon Matched Pairs Test (*mean $p > 0.05$, ± mean $0.05 < p > 0.01$, ¥$p < 0.01$). Global quality of life [valproate vs. lamotrigine; Mean ± SD] [45.7 ± 20.1 vs. 73.9 ± 15.5; $p = 0.000$ (t-test)]. Cognitive functioning [valproate vs. lamotrigine; Mean ± SD] [58.8 ± 26.5 vs. 79 ± 11.8; $p = 0.01$ (t-test)].

Table 5
Drug consumption rate and adverse events during treatment according to antiepileptic medication.

Consumption rate	LTG (%)[b]	Valproate (%)[b]
Consumption rate around 80%	3 (7.3)	2 (6.5)
Consumption rate between 90% and 100%	38 (92.7)	29 (93.5)
Side effects		
Percentage of patients with adverse events	7 (17.03)	11 (35,3)[a]
Tiredness/drowsiness/fatigue/lethargy	1 (2.4)	2(6.4)
Sleep disturbances	3(7.3)	1(3.2)
Ataxia	0	1(3.2)
Worsening of seizures (myoclonus)	1(2.4)	0
Behavior/personality change/aggression	1(2.4)	1(3.2)
Weight gain	0	5 (16.1)
Dyspepsia	1(2.4)	3 (9.7)
Diarrhea	0	1(3.2)
Abdominal pain	0	2(6.4)
Alopecia	0	3 (9.7)
Anovulatory cycles (amenorrhea)	0	2(6.4)
Subcutaneous edema	0	2(6.4)
Headache	1(2.4)	1(3.2)
Memory problems	0	1(3.2)
Weight loss	1(2.4)	0
Allergic rash	4(9.8)[††]	0
Tremor	0	2 (6.4)
Dizziness/vertigo	0	1(3.2)
Anxiety/agitation/nervousness	0	2(6.4)
Nausea	0	9 (29.1)

[a] Difference of adverse events presentation between drugs: chi squared test = 1.65; $p = 0.03$.
[b] Percentages are referred to the total of patients per group.
[††] Symbol is referred to the presentation of Stevens Johnson rash in two patients.

4.1. Possible methodological biases

Methodological biases could explain some of these differences, since dosing was left to the physician's usual practice and lower doses of VPA were used in females. Nevertheless, the doses were not disproportionately lower for women on VPA. In our study valproate was given three times a day. This may reduce compliance and account for the drop-out of some patients. Nevertheless, in this study this does not seem to be the case, as compliance measured by the number of pills taken every month was the same in both groups. On the other hand, patients with poor compliance were not eligible for the study. We must consider that the slower maximum dose escalation for LTG may have contributed to a better tolerability. However, this is the usual dose escalation recommended in other studies,[5–20] and reflects the dose escalation used for both medications (valproate and lamotrigine) in our common clinical practice.

Other possible methodological biases in our study could be related to selection preference due to the fact that this was an open label study which only had power to detect a fairly large difference in efficacy. In spite of the very different sample size enrolled for LTG and VPA, the randomization process worked as intended. This was due to patients' self decision, because some of them did not pick up their medication after they were randomized. Thus, more patients randomized to the valproate arm did not initiate the recommended treatment. Although we do not know exactly why this happened, the cause could be related to the adverse effect profiles discussed in their first visit, when the patients were enrolled. Thus, the discrepancy between the sample sizes of the two treatment arms could have affected the evaluation of safety and tolerability in our study.

Table 6
Differences among the subscales on the QOLIE-31 questionnaire at entrance and at the end of study according to groups of randomization.

QOLIE-31 (mean ± 2.5 SD)/medication	Lamotrigine	Valproate
Total QOLIE-31 score	7.3	12.3
Seizure worry	10.4	14.3
Emotional well-being	9.3	11.7
Energy/fatigability	12.5	12.5
Cognition functioning	5.3	11.4
Side effects of medication	−27.1	−35
Social functioning	10.9	8.3

Another methodological concern is how all seizure types were accurately counted, because it is well known that daily count of absence and myoclonic seizures could be inaccurate. That is why, all conclusions taking into account seizure rates, can be misleading. Nevertheless, our primary ending point was related to the time to withdraw treatment of any cause and to the time to achieve remission of all seizure types taking into account the normalization of the EEG recording (see Seizure Outcome Assessment in the Section 2). Thus, this methodological problem could be mitigated.

Another concern is the possible bias associated with the discontinuation of the medications that patients were taking before study entrance. This could affect the total count of seizures per month due to the possible increase in seizure frequency associated to clonazepam discontinuation or, the possible decrease in seizure frequency due to withdrawal of phenytoin or carbamazepine, which are antiepileptic drugs that induce myoclonic jerks. The follow-up of the patients for 8 weeks without any medication to evaluate their actual seizure rate at baseline would have been required; nevertheless, for ethical reasons it was not possible.

The unexpectedly low adverse event rates presented in our study (17% in the LTG arm and 35.5% in the valproate group) is another issue that should be discussed. We think that this result is related to how adverse events were defined and how they were detected/enquired at each visit. In the present study the adverse events were counted asking the subjects whether they felt any symptom after drug treatment was initiated. A structured questionnaire with all well known side effects of valproate and LTG would improve the detection of potential adverse effects. However, our method replicates what clinicians do in their everyday practice. Moreover, we did not assess the possible structural ovarian and hormonal changes in women taking part in this study, so we cannot comment on the endocrine side effects of the two drugs, which could also account for the relatively low rate of side effects found in our study.

To our knowledge, there are no randomized controlled studies that have directly compared valproate and lamotrigine monotherapy in a JME adult population. Therefore, we have no reliable evidence about the relative effectiveness of lamotrigine for taking clinical decisions in adults, especially for women of childbearing potential. The SANAD (Standard and New Antiepileptic Drug) study deserves a special mention. This study directly compared lamotrigine, topiramate and valproate in a well designed pragmatic, controlled, randomized, prospective study.[2] Nevertheless, none of the comparative analyses were carried out taking into account the different subtypes of IGE and it also included unclassified types of IGE syndromes. These aspects could differentiate our study from SANAD. For example, Jeavons Syndrome, one of the non-classified IGE syndromes, should be considered a myoclonic rather than an absence epilepsy, and this concept has therapeutic consequences, supporting the good clinical efficacy of antimyoclonic drugs such as levetiracetam and zonisamide[25] and some patients have also been reported to show resistance to lamotrigine therapy.[26,32] The above study also included persons of all ages.[2,25] Age could be an important factor for treatment response in IGE and patients with a longer time to diagnosis had a good response to LTG.[32–34] Nearly one-third of their patients with delayed diagnosis were initially treated with AEDs that were inappropriate for JME, including carbamazepine and phenytoin and they achieved a good response after changing to

LTG. As for the other patients, the delay in their diagnosis may be related to a benign clinical presentation, although the combination of seizure types was similar in patients with or without delayed diagnosis.[35] These variables could have played a role in our study, too.

One of the most important biases of our study could be that it was conducted by physicians in a tertiary center. Nevertheless, none of our patients was refractory to antiepileptic drugs, the electroclinical characteristics were typical of JME, the men/female ratio was similar to other studies[35–37] and the population in our tertiary center is not different from that of secondary or primary centers, because of the organization of health care in Cuba. For that reason, our study mainly reflects community based studies.

Another important concern is the power of the sample size calculation. In line with the objective of the more recent studies, our study is dedicated to demonstrate equivalence between lamotrigine and valproate. The design of equivalence trials differs from that of the traditional studies, aiming to detect differences in many important aspects. Fundamentally, instead of the conventional test for significance, statistical analysis is based on confidence intervals (CIs) that define a range for the possible true difference between the drugs.[1,38] Taking this paradigm into account, the two drugs under study can be regarded as equivalent if the entire CI for their difference lies within the pre-set clinically relevant range of equivalence. In our study we did not find differences between lamotrigine and valproate, considering CI for different primary end points (time to reach 50% of seizure control, time to withdrawal for any cause and time to achieve remission according to group of randomization). That is why, although we did not analyze the power of sample size calculation, this concern is mitigated by the objective of our investigation.

One of the most important cautions in prescribing lamotrigine in JME is the probability of myoclonic seizure worsening. This exacerbation in seizure rate, especially for myoclonic seizures, was reported by Fernando-Dongas et al.[39] and Biraben et al.[3] The later authors reported seven patients with myoclonus exacerbated by treatment with lamotrigine (LTG), four of whom were taking LTG monotherapy. This observation and our present results, where 1 (2.4%) of the patients experienced worsening of his seizure rate, raise concerns about the rationale of using LTG in the treatment of JME.

Because of possible hair loss, weight gain, and menstrual irregularities with valproate treatment, many physicians have used LTG as a first-line therapy in women with JME. Our positive experience with the drug contrasts with that reported by Biraben et al.[3] and slightly reflects the retrospective study of 24 patients with an established diagnosis of JME conducted by Carrazana et al.[10] In the Carrazana study seizure control was excellent (seizure freedom), although two of the 24 patients developed a dramatic exacerbation of myoclonus, leading to LTG therapy discontinuation.[37] An additional two patients had a mild increase in morning myoclonus, but it was transient, and sporadic GTCS continued in 2/24 patients (8.3%). In one patient, the occurrence of sporadic seizures was attributed to poor therapy compliance. Other investigators have reported similar positive experiences with the use of LTG for JME treatment.[40] The differences in the reported experience with LTG in JME may be due to a recruitment bias.

We agree that further studies are needed to establish the degree of efficacy and tolerability of LTG in the treatment of JME patients. We believe that, in the light of certain side effects of VPA treatment in female patients, LTG should be considered as an alternative option. Our experience suggests that exacerbation of myoclonus is seen in a small number of patients.

This observation is not in contradiction with the reports of a possible exacerbation of myoclonic seizures caused by LTG, because JME is most certainly a heterogeneous entity.[41,42] Keeping this variability in mind and owing to the fact that no simple test has been developed to identify these patients, we believe it is most important to emphasize the need for utmost prudence when using LTG in patients with JME.

4.2. Conclusion

According to ours results, lamotrigine is effective in adult patients with Juvenile Myoclonic Epilepsy and better tolerated than valproate. Thus, lamotrigine could be a treatment alternative for women with JME in developing countries, although the incidence of idiosyncratic reactions could be a concern.

Conflict of interest

None of the authors of the above manuscript has declared any conflict of interests.

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